Clinical Kidney Journal, 2022, vol. 15, no. 7, 1431–1433

https://doi.org/10.1093/ckj/sfac043
Advance Access Publication Date: 11 February 2022
Letter to the Editor



LETTER TO THE EDITOR

# Hypothyroidism-induced kidney dysfunction: an under-recognized phenomenon in patients on immune checkpoint inhibitors

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Acute kidney injury (AKI) during immune checkpoint inhibitor (ICI) therapy often raises concern for immune-related adverse events (irAE) [1]. A recent study reported ICI-induced thyroiditis to be a risk factor for acute and chronic kidney dysfunction, although the underlying etiologies and mechanisms were not fully elucidated [2]. We report an under-recognized cause of raised serum creatinine during ICI therapy, with diagnostic and therapeutic implications.

A 61-year-old Chinese female presented with a subacute creatinine rise after the initiation of Anti-programmed cell death protein 1 (anti-PD-1) for endometrial carcinoma, on a background of ICI-induced thyroiditis with resultant hypothyroidism 5 months after ICI initiation (Table 1). Urinalysis was bland and proteinuria was absent. Kidney imaging excluded obstruction but incidentally showed an atrophic right kidney. The C-reactive protein (CRP) level was normal. Thyroid function tests indicated ongoing hypothyroidism due to non-adherence to levothyroxine replacement. There was no evidence of rhabdomyolysis. Renal irAE was deemed unlikely and hypothyroidism-associated kidney dysfunction was suspected. Renal biopsy was deferred and the patient was counselled to improve medication adherence. ICI therapy was temporarily withheld but eventually not resumed. Serum creatinine returned to baseline following the restoration of euthyroidism (Figure 1a).

A 66-year-old Malay male was referred for raised serum creatinine 1 month after being diagnosed with immune-related hypophysitis, on the background of combination Anti-cytotoxic T lymphocyte-associated antigen-4 (Anti-CTLA-4) and anti-PD-1 therapy for renal cell carcinoma (Table 1). At presentation, he was on a physiological dose of hydrocortisone replacement for adrenal insufficiency from hypophysitis and was noted to have new-onset hypothyroidism due to immune-related thyroiditis. Urinalysis was bland and CRP was normal. Creatine kinase was mildly elevated but deemed insufficient to account for his AKI. A kidney biopsy was not performed in view of a history of nephrectomy. He was initiated on corticosteroids at 1 mg/kg for presumptive interstitial nephritis but did not exhibit a rapid improvement. Downtrend of creatinine was observed over the ensuing 3 months following levothyroxine replacement (Figure 1b).

Although kidney biopsy was not performed in these cases to confirm the cause of creatinine rise due to the presence of relative contraindications, their creatinine trends closely paralleled the course of their thyroid dysfunction, supporting the diagnosis of hypothyroidism-related kidney dysfunction. To our knowledge, our findings are corroborated by only one other report [3]. However, this phenomenon is likely under-recognized and under-reported. Thyroid dysfunction can either exert direct structural effects on the kidney or influence kidney function through cardiovascular and systemic hemodynamic perturbations [4]. The magnitude of creatinine rise seen is highly variable, although reported creatinine

Received: 9.2.2022; Editorial decision: 9.2.2022

**Table 1. Patient demographics and clinical characteristics**

| | Patient 1 | Patient 2 |
|---|---|---|
| Clinical presentation | | |
| Age/race/gender | 61/Chinese/female | 66/Malay/male |
| Oncological history | Endometrial carcinoma | Renal cell carcinoma |
| Date of immunotherapy initiation | 20 January 2020 | 28 November 2020 |
| Last dose of immunotherapy | 2 October 2020 | 11 January 2021 |
| Type of immunotherapy | Anti-PD-1 | Anti-CTLA-4/anti-PD-1 |
| History of non-renal irAE | Immune-related thyroiditis | Immune-related hypophysitis/ thyroiditis |
| Grade of non-renal irAE (CTCAE v5.0) | Grade 1 | Grade 3 |
| Date of diagnosis of non-renal irAE | 2 June 2020 (thyroiditis) | 25 March 2020 (thyroiditis) |
| Corticosteroid therapy at time of nephrology referral | No | Oral hydrocortisone 15 mg/day |
| Significant laboratory results | | |
| Baseline serum creatinine, μmol/L | 59 | 110 |
| Peak serum creatinine, μmol/L | 105 | 177 |
| Date of peak serum creatinine | 30 October 2020 | 1 April 2020 |
| Urine microscopy | Nil hematuria/pyuria | 3 red blood cells/IU 10 white blood cells/IU |
| Urine protein:creatinine ratio, g/g | 0.10 | 0.12 |
| TSH, MU/L[a] | 92.1 | 127 (Reference range: 0.65–3.7 MU/L) |
| fT4, pmol/L[a] | <3.2 | <3.2 (Reference range: 8.8–14.4 pmol/L) |
| fT3, pmol/L[a] | 1.9 | NA (Reference range: 3.2–5.3 pmol/L) |
| Creatinine kinase (U/L) | 243 | 1024 (Reference range: 44–201 U/L) |
| C-reactive protein (mg/L) | <0.6 | 0.6 (Reference range: 0.2–9.1 mg/L) |
| Kidney imaging | No obstruction in left kidney; right atrophic kidney from chronic obstruction | No obstruction in left kidney; history of right radical nephrectomy |
| Alternative causes of AKI[b] | Renal irAE deemed clinically unlikely | Unable to exclude renal irAE; empiric corticosteroids given |

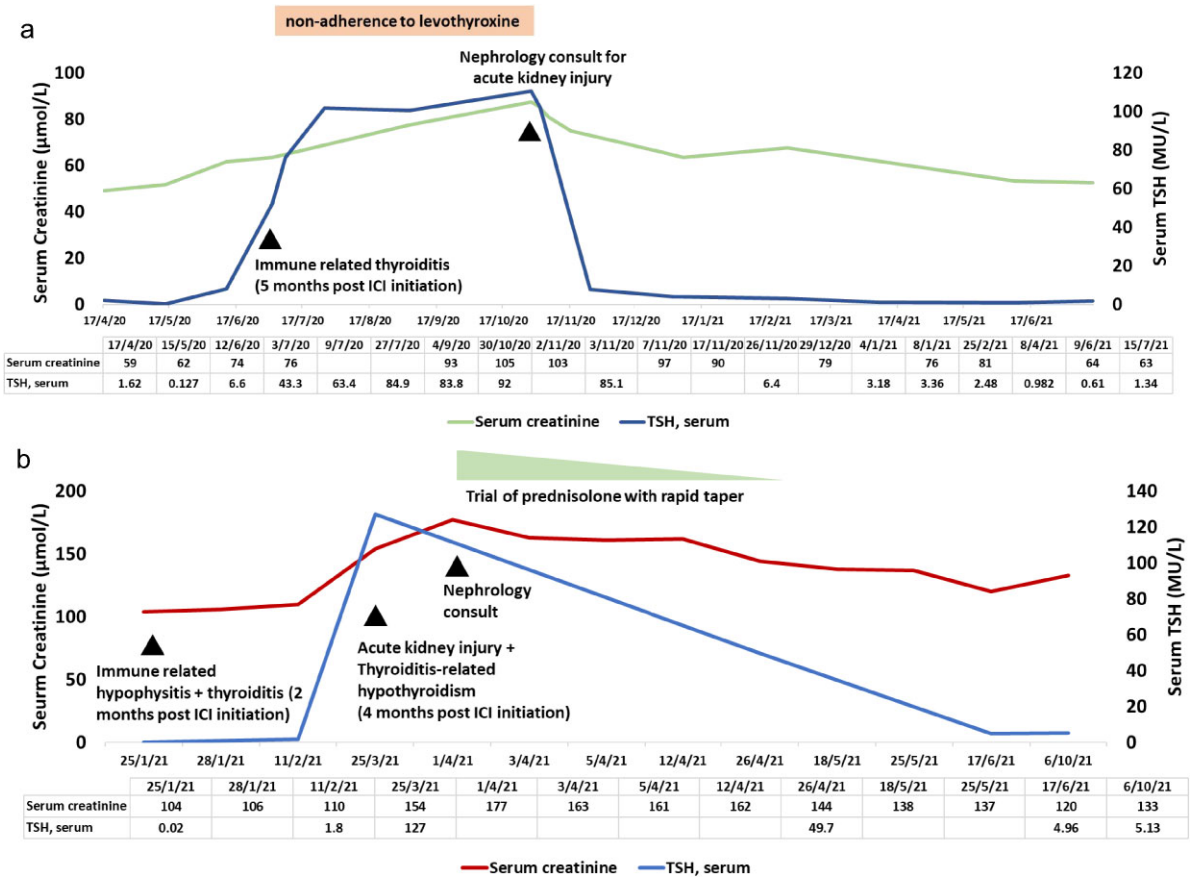
NA, not available; anti-PD-1, Anti-programmed cell death-1 inhibitor; anti-CTLA4, Anti-cytotoxic T lymphocyte-associated antigen 4; CTCAE (v5.0), Common Terminology Criteria for Adverse Events (v5.0); TSH, thyroid stimulating hormone; fT4, thyroxine; fT3, tri-iodothyronine; AKI, acute kidney injury; irAE, immune-related adverse events.

[a]Thyroid function tests at peak of kidney dysfunction.

[b]Auto-antibodies such as antinuclear antibodies, anti-double stranded DNA (anti-dsDNA), anti-myeloperoxidase and anti-proteinase 3 antibodies were not detected. Hepatitis B and C virologies were negative.

levels have been in the range of 1.5–2.5 mg/dL [4]. Cystatin-C levels are either normal or decreased in hypothyroid patients [3, 4]. Cystatin-C was unavailable and not performed in either case.

As thyroid irAEs are more common and generally occur earlier than renal irAEs, this phenomenon should be considered and prompt the concurrent evaluation of thyroid status when AKI occurs during ICI therapy. CRP has shown promise as a non-invasive biomarker for the early detection of selected irAEs [5, 6] and to discriminate between ICI related AKI from other causes [7]. Interestingly, the median CRP level was not elevated in ICI-thyroiditis in one series [5]. While elevated CRP by itself is not diagnostic of irAE due to its poor specificity, we propose that a non-elevated CRP may be used to discriminate between the different AKI etiologies in the right context, provided that the patient is not on corticosteroids exceeding physiological doses [7]. Hence, in patients with AKI and hypothyroidism, a normal CRP may favour the differential of hypothyroidism-induced kidney dysfunction in addition to a discrepant serum cystatin-C level, if available. After evaluation of alternative etiologies including rhabdomyolysis, expectant management may be considered in selected patients with close monitoring, if kidney dysfunction remains mild and non-progressive. Further research to validate our observation is required.




| | 17/4/20 | 15/5/20 | 12/6/20 | 3/7/20 | 9/7/20 | 27/7/20 | 4/9/20 | 30/10/20 | 2/11/20 | 3/11/20 | 7/11/20 | 17/11/20 | 26/11/20 | 29/12/20 | 4/1/21 | 8/1/21 | 25/2/21 | 8/4/21 | 9/6/21 | 15/7/21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serum creatinine | 59 | 62 | 74 | 76 | | | 93 | 105 | 103 | | 97 | 90 | | 79 | | 76 | 81 | | 64 | 63 |
| TSH, serum | 1.62 | 0.127 | 6.6 | 43.3 | 63.4 | 84.9 | 83.8 | 92 | | 85.1 | | | 6.4 | | 3.18 | 3.36 | 2.48 | 0.982 | 0.61 | 1.34 |

| | 25/1/21 | 28/1/21 | 11/2/21 | 25/3/21 | 1/4/21 | 3/4/21 | 5/4/21 | 12/4/21 | 26/4/21 | 18/5/21 | 25/5/21 | 17/6/21 | 6/10/21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serum creatinine | 104 | 106 | 110 | 154 | 177 | 163 | 161 | 162 | 144 | 138 | 137 | 120 | 133 |
| TSH, serum | 0.02 | | 1.8 | 127 | | | | | 49.7 | | | 4.96 | 5.13 |

FIGURE 1: (a) Trajectory of serum creatinine and thyroid function tests of Patient 1. (b) Trajectory of serum creatinine and thyroid function tests of Patient 2.

## CONFLICT OF INTEREST STATEMENT

JJC: Consulting or advisory role: Merck Sharp & Dohme. Travel sponsorship: Merck Sharp & Dohme. Rest of authors: No relevant conflicts of interest to declare.

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